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Review Article

New strategies for the treatment of hyperkalemia

Stefano Masi [a,*], Herman Dalpiaz [b], Sara Piludu [b], Federica Piani [c], Giulia Fiorini [c], Claudio Borghi [c,d]

[a] Department of Clinical and Experimental Medicine, University of Pisa, Italy
[b] Department of Surgical, Medical and Molecular Pathology and Critical Area, University of Pisa, Italy
[c] Hypertension and Cardiovascular Disease Research Center, Medical and Surgical Sciences Department, Alma Mater Studiorum University of Bologna, Italy
[d] Cardiovascular Medicine Unit, Heart-Chest-Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

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ABSTRACT

Renin-angiotensin-aldosterone system inhibitors (RAASi) and mineralocorticoid receptor antagonists (MRAs) are key drugs in the management of patients with cardiovascular diseases (CVD), particularly those with hypertension, diabetes, chronic kidney disease and heart failure (HF), given their demonstrated effectiveness in reducing the risk of both surrogate and hard endpoints. Despite their positive impact on the outcome, patients with RAASi and MRAs are particularly vulnerable to hyperkalaemia, with approximately 50 % of these individuals experiencing two or more recurrences annually. The common practice of reducing the dose or discontinuing the treatment with RAASi and MRAs in conditions of hyperkalaemia results in suboptimal management of these patients, with a potential impact on their mortality and morbidity risk. Recent guidelines from cardiovascular and renal international societies increasingly recognize the need for alternative strategies to manage the risk of hyperkalaemia, allowing the continuation of RAASi and MRA therapies. In this review, we summarise the new potential options available to manage hyperkalaemia in patients with CVD and the recommendations of the most recent guidelines on the topic.

1. Introduction

Potassium (K^+) is the most abundant cation in the body (50–75 mEq/L/kg body weight). Under physiological conditions, approximately 98 % of total body K^+ is located in the intracellular space and only 2 % in the extracellular space [1]. Several physiological and pathological processes regulate $K+$ metabolism, increasing or decreasing its body's content (Fig. 1).

1.1. POTASSIUM metabolism

1.1.1. Factors upregulating the body's $K^{\pm}$ concentration

The oral K^+ intake represents the primary source of potassium in the body, with significant differences between foods (fruits, vegetables, and meat contain the highest quantities of K^+). The intestine plays a crucial role in regulating K^+ metabolism through absorption and secretion processes. Potassium from dietary intake is primarily absorbed in the small intestine, especially in the jejunum and ileum, via both passive and active mechanisms [2]. Under normal circumstances, insulin and beta-adrenergic stimulation are important regulators of the K^+ distribution between intracellular and extracellular spaces. Insulin promotes cellular K^+ uptake, especially in muscle and liver cells, by stimulating the activity of the Na^+/K^+-ATPase pump [3]. After a meal, the increased circulating levels of insulin promoted by hyperglycaemia prevent hyperkalemia by driving K^+ uptake into cells, along with glucose. This process attenuates the postprandial increases in circulating K^+ levels, and explains at least in part the higher risk of hyperkalaemia in patients with a deficit of insulin signaling, such as those with diabetes mellitus [4]. In parallel with insulin, beta-adrenergic stimulation, mainly by beta-2 receptors, promotes K^+ uptake into cells by increasing the activity of the Na^+/K^+ ATPase pump [5]. While the adrenergic signal promoting K^+ uptake is, at least in part, mediated by the insulin release, beta-adrenergic stimulation has an indirect role also in the excretion of K^+, increasing renal blood flow, glomerular filtration rate and stimulating aldosterone secretion, a key regulator of K^+ excretion in the kidneys [5].

* Corresponding author at: Department of Clinical and Experimental Medicine, University of Pisa, Italy, Via Roma, 67, 560126 Pisa Italy.
E-mail address: stefano.masi@unipi.it (S. Masi).

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1.1.2. Factors downregulating the body's $K^{\pm}$ concentration

The kidneys are responsible for up to 90–95 % of K^+ elimination [4]. At this level, K^+ is excreted by the distal nephron's principal cells through mechanisms regulated by an electrochemical potential gradient [6]. Three factors can modulate the electrochemical potential gradient, either increasing or decreasing renal K^+ secretion. The first factor is the luminal flow in the distal nephron [7]. An increased luminal flow, obtainable under adequate, effective circulating volume, blood pressure, and renal perfusion pressure, creates a favourable gradient for K^+ secretion. In turn, reducing the luminal flow reduces the gradient for K^+ secretion, thus increasing the risk of hyperkalaemia. The second factor is the luminal sodium concentration, whereby a higher luminal sodium concentration, in physiological conditions, promotes K^+ secretion [8]. The third factor is the activity of the epithelial sodium channel (ENaC), mainly influenced by the circulating aldosterone levels [9]. Aldosterone enhances the number and efficiency of ENaC in the luminal membrane of the principal cells in the distal convoluted tubule (DCT), thereby facilitating K^+ secretion [10].

The remaining 5–10 % of K^+ excretion largely depends on the colon, although this proportion varies depending on the patient's clinical condition [2]. For example, the colonic excretion of K^+ increases when renal function worsens, so that in patients with end-stage renal disease, faecal K^+ secretion is three-fold higher than that of patients with normal renal function. The colon secretes K^+ into the intestinal lumen through a process that involves active transport mechanisms under the influence of aldosterone, which enhances K^+ secretion in exchange for sodium reabsorption.

1.2. Hyperkalaemia

Hyperkalaemia, defined as K^+ levels higher than 5.0 mEq/L, has an estimated prevalence of 6.3 % worldwide, with substantial differences between different countries [11]. In Asia, the prevalence is estimated at around 10.4 %, compared to 5.9 % in Europe and 5.0 % in North America. This difference can be due to a higher proportion of inpatients included in Asian studies, likely leading to an over-representation of subjects with impaired renal function. Also, the higher K^+ content in the diet of Asian populations compared to other regions might contribute to the higher prevalence of hyperkalaemia in Asia [11].

Hyperkalaemia can be classified as mild (>5.0 to <5.5 mEq/L), moderate (>5.5 to <6.0 mEq/l) or severe (>6.0 mEq/L) [12]. Severe hyperkalaemia can be considered a clinical emergency as it is associated with a higher risk of arrhythmic events and sudden deaths, resulting not only in an increased mortality risk but also in a significant increase in the morbidity and hospitalization burden. Although the absolute circulating K^+ levels are the strongest determinants of the morbidity and mortality risk associated with hyperkalaemia, the evidence that also patients with mild-to-moderate hyperkalaemia have an increased risk of arrhythmic complications related to elevated levels of K^+ emphasizes the importance of considering the circulating concentrations of K^+ in the context

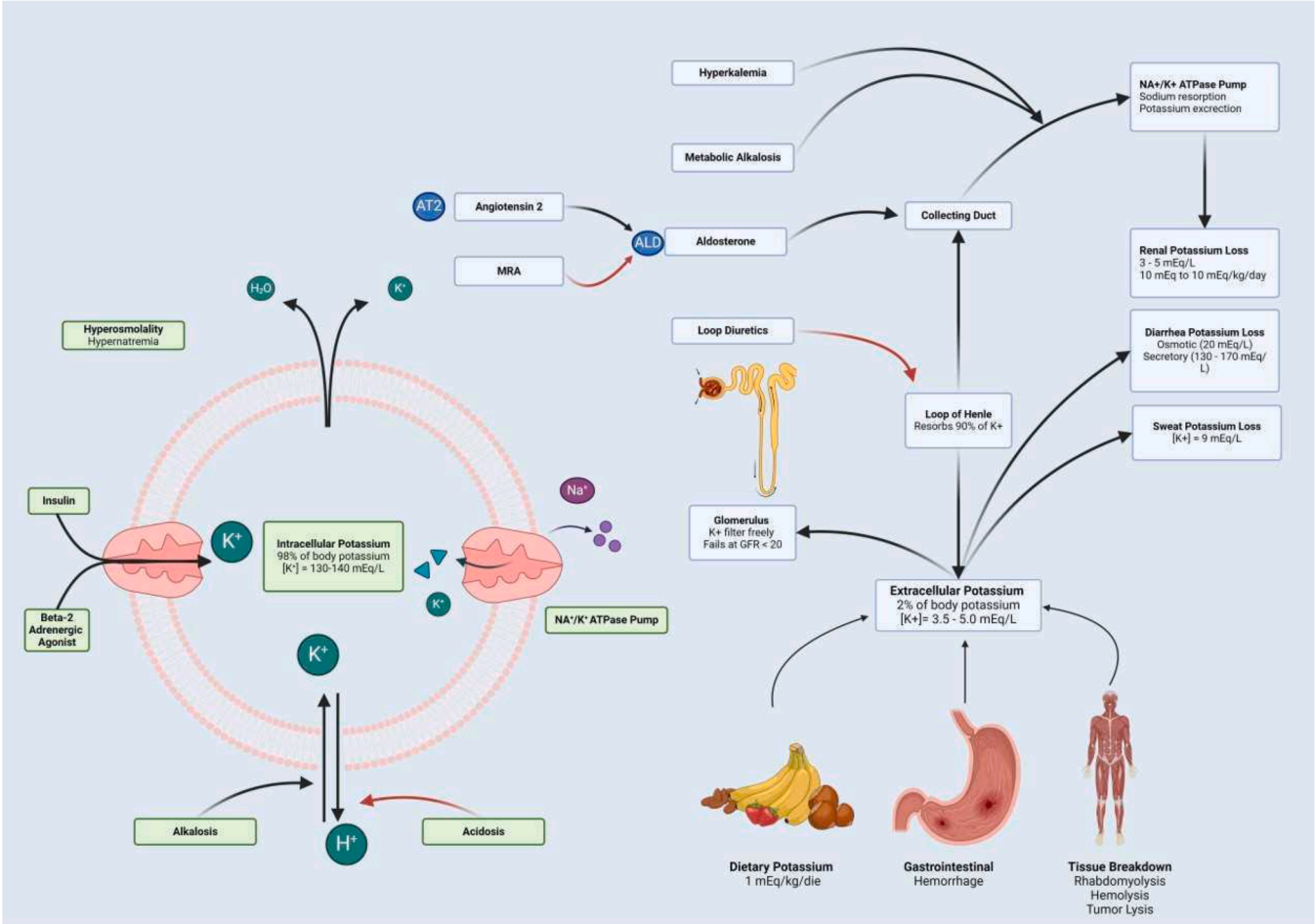

Fig. 1. Iconographic representation of the $K+$ metabolism. K^+ is the second most abundant cation in the body (~3.5 mol). 70 – 150mEq/day of K^+ derives from the diet. Once absorbed, K^+ is rapidly moved to the intracellular fluids from the extracellular spaces. The insulin and β-adrenergic signals stimulate the activity of the membrane Na^+/K^+-ATPase, which promotes the shift of K^+ into cells. In turn, in conditions of hyperkalaemia and acidosis, $K+$ is excreted from the intracellular to the extracellular space in exchange with hydrogen ions. The kidney represents the most important organ removing K^+ from the body, and 90 % of K^+ is reabsorbed at the level of the loop of Henle. This reabsorption is counteracted by loop diuretics that promote hypokalaemia. Created with Biorender.

of the patient's clinical conditions. Indeed, beyond the absolute K^+ levels, the risk of complications related to hyperkalaemia also depends on the more or less rapid increase in the circulating K^+ concentrations and the duration of the hyperkalaemia [13]. Generally, patients with rapid elevation of K^+ levels and shorter duration of hyperkalaemia are at higher risk of hyperkalaemia-related arrhythmic events. In addition, it has been observed that the probability of undergoing episodes of hyperkalaemia progressively increases with the number of previous hyperkalaemic events, and the interval between consecutive events tends to shorten over time. In a retrospective, observational cohort study on primary and secondary care data from Clinical Practice Research Datalink including 931,460 patients with chronic kidney disease (CKD) stage 3+, heart failure (HF), resistant hypertension, dialysis, diabetes, and/or renin-angiotensin-aldosterone system inhibitors (RAASi), 310, 535 (33.3 %) patients experienced ≥ 1 hyperkalaemia event and 187.719 (20.2 %) experienced hyperkalaemia recurrence, the risk of which increased from 60.5 % for the second event to 76.5 % for the sixth event [14]. In another population-based cohort of 31,649 patients with incident HF from northern Denmark, 39 % of patients experienced at least one episode of hyperkalemia over a mean follow-up of 2.2 years, and the risks of experiencing a second, third, or fourth event were 43 %, 54 %, and 60 %, respectively [15]. Risk factors for the development of hyperkalaemia included CKD, diabetes mellitus, and spironolactone use [15]. In the REVOLUTIONIZE I real-world study based on de-identified electronic health record data from patients with CKD (stage 3–4) and an episode of hyperkalemia within 30 days before recruitment, 56.0 % of patients had ≥ 1 hyperkalemia recurrence and 37.4 % had ≥ 1 recurrence within the first month of follow up. The average time to first hyperkalemia recurrence was 45 days, with the time between recurrences decreasing with subsequent episodes [16]. This data suggests that the treatment of hyperkalaemia should be personalized, considering not only the absolute K^+ levels but also the causes, rate of development and duration of the clinical condition leading to an imbalance in the K^+ metabolism.

1.3. The risk of hyperkalaemia along the cardiovascular disease continuum: from hypertension to heart failure

Hyperkalaemia is one of the most common electrolytic disorders in patients with risk factors or established cardiovascular diseases (CVD). Although drugs commonly used in patients with CVD can increase the risk of hyperkalaemia, the higher prevalence of CVD in older people and their association with comorbidities predisposing to the elevation of K^+ levels also contribute to the risk of hyperkalaemia in this population. Indeed, ageing, diabetes and hypertension (risk factors that frequently coexist with CVD) lead to a progressive decline of renal function while promoting the evolution of the CVD continuum towards HF [4]. When HF ensues, the reduced kidney perfusion associated with the impaired left ventricular systolic or diastolic function might represent a further contributor to the development of hyperkalaemia [4,17]. While these factors progressively increase the risk of hyperkalaemia along the evolution of the CVD continuum, acute states of dehydration or sepsis that worsen tissue perfusion leading to metabolic acidosis can rapidly deteriorate the electrolyte balance, leading to a sudden increase in the circulating K^+ levels also in patients with long-standing, well-tolerated therapies. For example, hot seasons and acute illness associated with vomiting and diarrhea represent acute causes of dehydration that can rapidly increase K^+ levels in older and frail subjects under diuretic therapies. This emphasizes the challenge in maintaining an accurate fluid balance, particularly in patients with established HF in whom excessive fluid overload can cause acute decompensation of the disease, while an excessive diuretic therapy might impair renal function and promote hyperkalaemia. It also highlights the importance of ensuring adequate hydration with i.v. fluids in the management of patients with acute hyperkalaemia.

Arterial hypertension is the most common risk factor for CVD [18]. Its prevalence increases with age and is characterized by an accelerated arterial wall stiffening, ultimately leading to a higher risk of renal microvascular damage and functional impairment. The recommendation of starting blood pressure lowering therapy with combinations of antihypertensive medications in most patients with hypertension, as reported in the European hypertension guidelines [19], provides a practical instrument to mitigate the risk of hyperkalaemia related to the prescription of RAASi. Indeed, the combination of these drugs with thiazide diuretics which, in turn, increase the K^+ renal excretion, can substantially reduce the hyperkalaemia risk related to RAASi. Consequently, the prevalence of hyperkalaemia associated with the use of RAASi in patients with hypertension and normal renal function is low [20] and often limited to patients with increased intrarenal vascular resistance. In these conditions, a mild decline in the glomerular filtration rate, potentially associated with an elevation of circulating K^+ levels, might be observed following the initiation of RAASi [20,21]. Such an increase in K^+ levels is usually modest, reversible, and rarely requires specific treatment. Chang et al. recently evaluated the association between the prescription of antihypertensive medications and the prevalence of hyperkalemia over three years in a cohort of 194,456 outpatients. They found that K^+ levels >5 mEq/L occurred in 10.8 % of patients, with the most common change in the treatment regimen being the discontinuation or dose reduction of RAASi [22]. A comprehensive retrospective analysis of a large electronic medical records database encompassing 201,655 patients with cardiorenal comorbidities documented a similar approach to patients developing hyperkalaemia, showing that a significant portion of hyperkalemia events (serum K^+ $\geq$5.1 mEq/L) resulted in the discontinuation or down titration of RAASi [23].

In patients with resistant hypertension the risk of hyperkalaemia is substantially increased. Resistant hypertension is defined as uncontrolled blood pressure values despite the use of three classes of antihypertensive medications that include a diuretic [19]. When the diagnosis of resistant hypertension is confirmed through the use of out-of-office methods, mainly ambulatory blood pressure monitoring (ABPM), the current hypertension guidelines recommend using spironolactone on top of the standard antihypertensive treatment with RAASi, Ca-channel blockers and thiazide-type/thiazide-like diuretics [19]. This recommendation is based on the results of the PATHWAY-2 trial, showing the superiority of spironolactone in reducing blood pressure in patients with resistant hypertension compared to alfa-blockers and beta-blockers [24]. Mineralocorticoid receptor antagonists (MRAs), however, are known to increase the risk of hyperkalaemia substantially. Such a risk is further increased by the common coexistence of comorbidities in patients with resistant hypertension that can contribute to worsening the blood pressure control but also increase the impact of hyperkalaemia through impairment of renal function [25]. For example, diabetes is often associated with both resistant hypertension and impaired kidney function, increasing the risk of hyperkalemia in patients with resistant hypertension [25]. As such, hyperkalaemia is highly prevalent in patients with a diagnosis of resistant hypertension. In a study by Khosla et al., the prevalence of hyperkalaemia in patients starting MRAs for resistant hypertension and with mild reduction of renal function (mean estimated glomerular filtration rate, eGFR: 56.5 $\pm$ 16.2 ml/min/1.73 m^2) was 17.2 %, with the baseline eGFR and the extent of blood pressure reduction achieved after MRA treatment representing the most important predictors of hyperkalaemia episodes [21]. Notably, the highest risk of hyperkalaemia in patients with hypertension starting MRAs is observed in the first few weeks from the treatment initiation. In a study including 6575 patients with hypertension who achieved good blood pressure control after MRA prescription, the incidence of hyperkalaemia in the presence or absence of CKD was 50.4 and 42.6 %, respectively, after 4 weeks and 3.8 and 3.0 % after 8 weeks [26].

The prevalence of hyperkalaemia in patients with resistant hypertension is similar to the one recorded in patients with HF, likely because these two conditions share common risk factors and treatment

strategies.

Clinical trials in HF patients have reported variable rates of hyperkalemia (Table 1). During the SOLVD trial, 7.8 % of patients treated with enalapril developed hyperkalemia (defined as K^+ levels >5.5 mEq/l) [27]. A lower prevalence of hyperkalaemia was recorded in the CHARM trial, with an incidence of 5.5 % in the candesartan arm [28]. In turn, the concomitant prescription of MRAs with RAASi increases the risk of hyperkalaemia. In the RALES trial, combining angiotensin-converting enzyme inhibitors with spironolactone, K^+ levels >5.5 mEq/l were reported in 19 % of patients, increasing to 51 % when hyperkalaemia was defined based on a cut-off of K^+ >5 mEq/l [29]. Given that randomized clinical trials reflect a clinical experience obtained in a highly controlled environment, the risk of hyperkalaemia reported in this setting might not reflect the one observed in real life. In a large population of patients treated with ACE inhibitors and recently hospitalized for HF in Ontario, Canada, Juurlink et al. documented a significant increase in the spironolactone-prescription rate after the publication of RALES, which was paralleled by a substantial increase in the rate of hospitalization and mortality for hyperkalemia [30]. However, further analyses were able to document that these findings were likely attributable to the widespread inappropriate prescription of MRAs [30,31]. In the SwedeHF (Swedish HF) registry, 24.4 % of 5848 patients with HF experienced hyperkalemia (K > 5.0 mmol/l) at least once, and 10.2 % had moderate or severe hyperkalaemia (K > 5.5 mmol/l) [32]. A higher prevalence of hyperkalaemia was observed in the Clinical Practice Research Datalink (CPRD) in the UK, showing that amongst 21,334 HF patients, 7648 (35.9 %), 2725 (12.8 %), and 763 (3.6 %) experienced episodes of serum K^+ ≥ 5.0, ≥ 5.5, and ≥ 6.0 mmol/L respectively, over a follow-up of about 5 years [33]. The discrepancy in the described incidence and prevalence of hyperkalaemia across different observational studies emphasizes that, in daily clinical practice, the risk of hyperkalaemia related to MRA and RAASi prescription might be influenced by the experience of the physicians, local guidelines, the complexity of the clinical presentation and the availability/quality of HF services in a specific community. With this regard, a recent survey of the Heart Failure Association of the European Society of Cardiology has demonstrated that hyperkalaemia represents the third most frequently perceived clinical barrier to the implementation of guidelines recommended therapy in patients with HF, immediately after hypotension and creatinine increase [34].

1.4. New strategies for the treatment of hyperkalaemia in patients at different stages in the evolution of the cardiovascular disease continuum

New treatment strategies are available in patients with or at high risk of developing hyperkalaemia. While some of these strategies are based on drugs specifically prescribed to reduce K^+ levels, others take advantage of the ancillary effects of medications prescribed for other indications in patients treated with RAASi and/or MRAs.

1.4.1. Potassium binders

The new K^+ binders are recommended by the European Heart Failure guidelines and suggested in the European Hypertension guidelines as a helpful treatment to reduce the risk of hyperkalaemia in patients requiring optimization of RAASi or MRA treatment [19,35]. These include patiromer and sodium zirconium cyclosilicate (SZC). Table 2 reports the main characteristics of these two drugs.

Patiromer is a polymer that binds the free K^+ ions in the gastrointestinal tract (mainly in the distal colon lumen) (Fig. 2). Given this mechanism of action, its efficacy in reducing the circulating K^+ concentration is particularly relevant in patients with CKD and hyperkalemia because of the upregulated secretion of K^+ into the colon in these patients. Its K^+-binding capacity and tolerability are higher than the polystyrene sulfonate polymer [36].

In the AMBER trial, the use of patiromer enabled more patients with resistant hypertension and CKD (eGFR 25 to ≤45 mL/min/1.73 m^2) to continue treatment with spironolactone with lower incidence of hyperkalaemia [37]. In two separate subgroup analyses of the same trial, patiromer reduced the risk of hyperkalaemia, thus enabling more persistent use of spironolactone, in patients with HF or with an eGFR below 30 ml/min/1.73 m^2 [38,39].

In the PEARL-HF trial, including patients with HF and CKD but with normal K^+ levels, the treatment with patiromer facilitated the spironolactone dose titration, also reducing mean serum K^+ level by 0.45 mmol/L compared to placebo and the risk of hyperkalemia events [40]. Among patients with HFrEF and history of hyperkalemia included in the DIAMOND study, the treatment with patiromer was associated with lower serum K^+ levels and lower incidence of severe hyperkalemia (>5.5 mEq/L) compared with control. Furthermore, 85 % of participants in the patiromer arm reached the optimal dose of guideline-directed RAASi treatment [41]. Finally, the AMETHYST-DN trial observed encouraging results in diabetes patients with CKD (stage 3–4) who received RAASi and had mild or moderate hyperkalemia [42].

In all the major trials, gastrointestinal (GI) side effects (including constipation, flatulence, and diarrhoea) are the most common adverse events reported in patients using patiromer, with an incidence of <10 %. The onset of GI adverse events usually occurs within the first 4 weeks of treatment. Beyond the GI symptoms, the treatment with patiromer has been associated with reduced magnesium levels and increased serum calcium levels in rare cases [43], with a potential dose-response relationship (higher doses of patiromer were associated with a higher incidence of hypomagnesemia in the AMETHYST-DN trial [42]). Finally, hypokalemia defined as serum K^+ < 3.5 mEq/L is a rare but potential complication during treatment with patiromer [44].

Sodium Zirconium Cyclosilicate (SZC) is a non-polymer compound that acts as a selective cation exchange agent throughout the gastrointestinal (GI) tract, exchanging hydrogen and sodium ions for K^+. This increases K^+ faecal excretion without impacting magnesium and calcium concentrations (Fig. 2).

The PRIORITIZE-HF was the largest published trial of SZC in patients with CVD [45]. The enrolled patients had HFrEF and hyperkalemia at baseline or were at risk of hyperkalemia. The COVID-19 pandemic significantly affected the trial conduction, with only 182 of the planned 280 participants randomized, and one-quarter of those did not complete the 12-week follow-up. Given these difficulties, the trial was terminated early because of the inability to complete study visits during the pandemic. A further complication in the interpretation of the results derives from the evidence that the risk of developing hyperkalemia in the placebo group was lower than anticipated, likely due to a limited optimization of RAASi therapy for clinical inertia (the management of RAASi or MRA therapy was left to the site investigators). With all these limitations, no difference in the prescription of RAASi was observed between the SZC and placebo arms. Other trials that demonstrated SZC to lower K^+ levels were not specifically designed to target populations of patients with hypertension or CVD. In the HARMONIZE trial, within the subgroup of patients with HF (n = 94), SZC lowered K^+ levels to <5.0 mEq/L in 93 % of participants within 48 h [46]. More recently, the study design and baseline characteristics of the RALIZE-K trial were published. This prospective, double-blind, placebo-controlled trial included patients with HFrEF (NYHA functional class II-IV; left ventricular ejection fraction ≤40 %), already treated with optimal medical therapy (except MRAs) and prevalent hyperkalemia or at high risk of developing hyperkalaemia. In an open-label run-in phase of the trial, all participants underwent a protocol-mandated titration of spironolactone, targeting a dose of 50 mg daily. Patients with baseline or acquired (during the titration phase) hyperkalaemia started SZC. Participants who achieved normokalemia while taking spironolactone at a dose of 25 mg or more daily were randomly assigned to either continue taking SZC or a matching placebo for 6 months. The primary composite endpoint is the proportion of participants continuing the guideline-recommended therapy (spironolactone at a dose of 25 mg or more daily) with normokalemia and without needing rescue treatment for hyperkalemia during the first 6 months of treatment [47].

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Table 1
Summary of heart failure studies reporting rates of hyperkalaemia associated with the use of renin-angiotensin-aldosterone system inhibitors.

Trial	Population	Mean Age	Gender	NYHA Classification	Comorbidities	Renal Function (eGFR or Creatinine)	Patients with Renal Impairment (%)	Treatment	Duration of Study	Key Results	Incidence of Hyperkalemia	Mean Increase in Potassium Levels	Common Side Effects
SOLVD [27]	2569 patients with left ventricular dysfunction FE < 35 %	~60 years	75 % male, 25 % female	II: 55 %, III: 35 %, IV: 10 %	Hypertension: 60 %, Diabetes: 30 %	Mean creatinine 110–130 μmol/L, trend of worsening with enalapril	About 15–20 % (patients with pre-existing renal impairment)	Enalapril (10–20 mg/day) Placebo	3 years	27 % reduction in overall mortality; 25 % reduction in morbidity.	1.5 %	+0.5 % to +1.0 %	Hypotension: 10 %, Dry cough: 5 %
CHARM [28]	7601 patients with heart failure	~65 years	70 % male, 30 % female	II: 50 %, III: 40 %, IV: 10 %	Impaired renal function: 40 % Diabetes: 25 %	Average eGFR between 55 and 60 ml/min/1.73m^2	About 20 % with eGFR <60 ml/min	Candesartan (4–32 mg/day) Placebo	3.5 years	15 % reduction in mortality; 20 % reduction in heart failure hospitalizations.	1.5 %	+0.4 % to +1.0 %	Hypotension: 9 %, Hyperkalemia: 1.5 %
RALES [29]	1663 patients with heart failure	~65 years	70 % male, 30 % female	II: 60 %, III: 30 %, IV: 10 %	Hypertension: 50 %, Renal insufficiency: 20 %	Mean creatinine 100–150 μmol/L and worsened in some patients	About 30 % with renal impairment	Spironolactone (25–50 mg/day) Placebo	2 years	30 % reduction in mortality; 35 % reduction in hospitalizations.	2 % (spironolactone)	+1.0 % to +1.5 %	Hypotension: 10 %, Hyperkalemia: 2 %
SwedeHF Registry [32]	40,000 patients with heart failure	~75 years	60 % male, 40 % female	II: 40 %, III: 40 %, IV: 20 %	Chronic renal insufficiency: 25 % Diabetes: 30 %	Creatinine and eGFR variable, many patients with eGFR <60 ml/min	About 25–30 % with renal impairment	ARAs, Beta-blockers, Diuretics	5 years	Hyperkalemia associated with ARA therapy; Improvement in quality of life.	2.2 % (ARAs)	+0.6 % to +1.2 %	Hypotension: 5 %, Hyperkalemia: 2 %
CPRD (UK) [33]	>500,000 patients with heart failure	~70 years	65 % male, 35 % female	II: 45 %, III: 35 %, IV: 20 %	Multiple comorbidities: 50 % Diabetes: 25 %	eGFR and creatinine data monitored nationwide, many patients with eGFR <60 ml/min	About 20–25 % with reduced renal function	ARAs, Beta-blockers, Diuretics	5 years	Increased incidence of hyperkalemia by 3.5 % in patients on ARAs.	3.5 % (ARAs)	+1.0 % to +1.8 %	Hypotension: 10 %, Edema: 5 %

Table 2
Dosages, clinical and potential side effects of patiromer and sodium zirconium cyclosilicate (SZC).

Feature	Patiromer	Sodium Zirconium Cyclosilicate
Dosage	Initial: 8.4 g once daily	Initial: 10 g three times a day
	Maintenance: 8.4 g to 25.2 g once daily	Maintenance: 5 g to 15 g once daily
Administration	Oral suspension (mixed with water)	Oral suspension (mixed with water)
Onset of Action	~7 h (peak effect in 24 h)	~1 hour (peak effect in 24 h)
Expected Results	Lowers serum potassium levels by ~1.0 mEq/L in 1 week	Lowers serum potassium levels by ~1.0 to 1.5 mEq/L in 48 h
Common Side Effects	- Constipation	- Edema
	- Diarrhea	- Nausea
	- Nausea	- Vomiting
	- Abdominal discomfort	- Constipation
Serious Side Effects	- Hypomagnesemia	- Edema
	- Gastrointestinal obstruction	- Hypokalemia
Contraindications	- Severe constipation	- Bowel obstruction
	- Bowel obstruction	- Known hypersensitivity
Monitoring	Regular monitoring of potassium and magnesium levels	Regular monitoring of potassium levels

1.4.2. Other strategies to mitigate the risk of hyperkalaemia in patients requiring RAASi/MRAs therapies

Ancillary properties of several drugs that are commonly prescribed in patients with HF might mitigate the risk of hyperkalaemia in this population. For example, in the PARADIGM-HF, the incidence of severe hyperkalaemia was lower when the RAASi treatment was associated with sacubitril (i.e. in the sacubitril/valsartan arm) compared to the one observed in the enalapril arm (4.3 % versus 5.6 %) [48]. In a follow-up analysis of PARADIGM-HF, sacubitril/valsartan did not affect K^+ levels overall, and patients on this therapy experienced a slight reduction in K^+ levels compared to those on enalapril, particularly when enalapril was combined with an MRAs [49]. Another example of drugs reducing the risk of hyperkalaemia in patients with HF while prescribed for indications other than reduction of the K^+ levels is provided by the sodium-glucose cotransporter 2 inhibitors (SGLT2i). These drugs either cause no effect or a slight reduction in plasma K^+ concentration in patients with normal kidney function but seem to exert a protective effect against hyperkalemia in the setting of reduced kidney function or when given with RAASi. In a meta-analysis of randomized clinical trials including patients with type 2 diabetes, SGLT2i reduced the risk of serious hyperkalemia by 16 %. Notably, reductions in serious hyperkalemia were observed across subgroups, including baseline kidney function, history of HF, and use of RAASi, diuretic, and MRAs [50]. Similar results were obtained in a pooled analysis of HF patients with reduced or preserved ejection fraction included in the EMPEROR programme, where empagliflozin reduced the composite of investigator-reported hyperkalemia or initiation of K^+-binding drugs without increasing the incidence of hypokalemia [51]. Probably related to the reduced risk of hyperkalaemia, the concomitant treatment with SGLT2i has been shown to reduce the risk of MRAs discontinuation in the EMPEROR-reduced trial [52], providing another potential mechanism by which these drugs could have a positive impact on the outcome of patients with HFrEF.

Finally, finerenone, a new non-steroidal MRA with proven cardioprotective effects in patients with diabetic nephropathy, has been claimed to reduce the risk of hyperkalaemia compared to traditional steroidal MRAs when combined with RAASi. A meta-analysis of clinical trial data documented a lower relative risk of hyperkalaemia when the

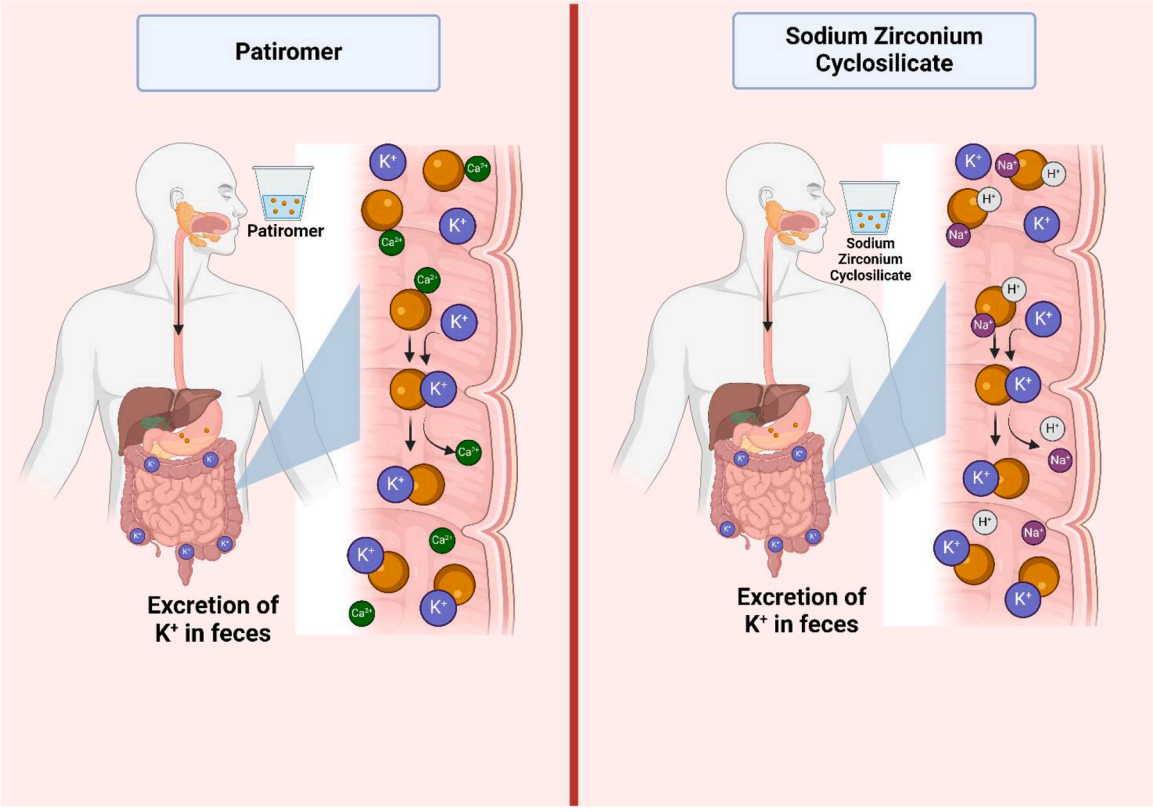

Fig. 2. Patiromer and Sodium Zirconium mechanisms of action. Sodium zirconium cyclosilicate and patiromer bind K^+ in the GI lumen in exchange for H^+, Na^+ and Ca^{+}, respectively, allowing more K^+ excretion.

ACEi/ARB treatment was combined with finerenone than with eplerenone or spironolactone in patients with diabetic nephropathy [53]. Similarly, in an indirect comparison of clinical trial data, Agarwal et al. suggested lower rates of moderate/severe hyperkalaemia in patients treated with finerenone (11.6 %) than those treated with spironolactone and a $K+$ binder (35.4 %) [54]. Despite these promising results, in placebo-controlled clinical trials the use of finerenone remains associated with an increased risk of hyperkalaemia. Indeed, in the pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials (FIDELITY), treatment with finerenone was associated with higher rates of serious hyperkalaemia, hyperkalaemia, and permanent discontinuation of the drug due to hyperkalaemia, as compared to placebo [55]. As expected, patients with more severe impairment of the eGFRs had a higher risk of hyperkalaemia [56,57]. Also in the FINEARTS trial, including 6001 patients with symptomatic HF (NYHA class II-IV) and LVEF $\geq$40 %, finerenone significantly increased the incidence of serum potassium >5.5 mmol/L (14.3 %) compared with placebo (6.9 %) [58]. Remarkably, there was no significant difference in the percentage of patients experiencing a sustained deterioration of the renal function (eGFR decrease $\geq$50 % or to <15 mL/min/1.73 m^2, new dialysis requirement, or kidney transplantation) in the finerenone or placebo groups [58], at variance with what was observed in the FIDELIO-DKD where patients treated with finerenone had a reduced progression of diabetic chronic kidney disease [59]. A new individual patient level meta-analysis accompanying the publication of the FINEARTS results and exploring the effect of MRAs in patients with heart failure across the full range of ejection fraction documented that the incidence of hyperkalaemia was doubled in patients treated with MRAs vs placebo, without differences between steroidal and non-steroidal MRAs [60]. Based on these results, therefore, the suggested reduction in the risk of hyperkalaemia related to the use of finerenone vs other MRAs should be confirmed by further, large randomized clinical trials.

1.5. The recommendations of the guidelines

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for diabetes management in CKD [61], the KDIGO guidelines for blood pressure management in CKD [62], the ESC Heart Failure guidelines [35], the European Society of Hypertension guidelines [19] and the American College of Cardiology (ACC) Heart Failure guidelines [63] contain recommendations on the management of hyperkalemia. Beyond guidelines, consensus recommendations [64] from national [65,66] and international [67] societies/associations provide specific suggestions on how to manage hyperkalemia in patients RAASi.

On some occasions, the messages provided by different guidelines might considered confusing. For example, while the ESC Heart Failure guidelines recommend initiating pharmacological K^+-lowering treatment with $K+$ binders as soon as serum K^+ exceeds 5.0 mmol/L [35], the ACC Heart Failure guidelines advocate a higher threshold for identifying hyperkalemia (serum $K^+ \geq$ 5.5 mmol/L) [63]. Furthermore, while the ESC Heart Failure guidelines emphasize the importance of continuing RAASi also in patients with hyperkalaemia, suggesting to reduce or discontinue this treatment only in patients whose serum K^+ exceeds 6.5 mmol/L, the ACC Heart Failure guidelines highlight that the effect of this treatment continuation on cardiovascular outcomes in patients with hyperkalaemia remains uncertain [63]. In keeping with the message provided in the ESC Heart Failure guidelines, the KDIGO guidelines and several international consensus documents on the management of hyperkalemia recommend that RAASi treatment should be de-escalated or discontinued only if alternative measures for hyperkalemia management have been optimized but failed to normalize serum K^+[61,62,64]. Potassium-wasting diuretics may be considered for patients with extracellular volume expansion. At the same time, oral supplementation with sodium bicarbonate can be used in patients with metabolic acidosis. However, the use of diuretics necessitates careful monitoring to prevent hypovolemia or deteriorating renal function. In contrast, prolonged sodium bicarbonate supplementation may increase sodium load, potentially worsening fluid overload in patients with CKD and HF [67].

The ESC, ACC, international consensus recommendations, and the UK Renal Association recommend using new K^+ binders (i.e., patiromer and SZC) to manage hyperkalemia while maintaining RAASi /MRA treatments [35,63,64,67]. A multidisciplinary panel of cardiologists and nephrologists has recently proposed two pragmatic diagnostic and therapeutic algorithms to optimize the use of the new K binders in stable adults who require treatment with RAASi and experience hyperkalaemia [68].

2. Conclusions

Hyperkalemia is a common finding along the cardiovascular disease continuum and is associated with adverse health outcomes, increased morbidity and mortality. Early diagnosis and understanding of the underlying causes are crucial for appropriate patient management. Given the diverse mechanisms contributing to hyperkalemia, a multidisciplinary approach is necessary to optimize the patient's management and reduce the risk associated with this condition. Several effective and safe therapeutic options exist for treating hyperkalemia across different patient groups. However, there are still gaps in our knowledge related to the long-term capacity of novel potassium binder treatments to effectively reduce the mortality and morbidity risk across the cardiovascular disease continuum, by enabling optimization of the medical therapy, making ongoing research essential to enhance our understanding of their potential impact on the patient outcome.

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Declaration of interests

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